DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/13/2010 has been entered.

Claims 1,9-16,18-21,23 and 27-28 are amended. Claims 2-8,17 and 22 are cancelled. Claims 24-26 are withdrawn.

Claims 1,9-16,18-21,23-28 are pending. Claims 1,9-16,18-21,23,27 and 28 are under consideration in the instant office action.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27 and 28 remain rejected and claims 1,9-16,18-21,23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method of treatment wherein the disorder is a cardiac myopathy resulting from myocardial infarction and wherein the cells used are skeletal myoblasts or synovial cells, and for the recited product wherein are not ES cells does not reasonably provide enablement for any cardiac disorder other than that resulting from cardiac infarction or for use of any cell type other than skeletal myoblasts or synovial cells, including a single synovial cell or for the product as claimed when the cells are ES cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The nature of the invention relates to the formation of a sheet of cells on a temperature responsive polymer that allows for removal of the cell sheet from culture upon a shift in temperature. This avoids the use of chemical and/or enzymatic cell dissociation and preserves cell-cell interactions. A brief review of the state of the art of temperature responsive cell culture polymers is in Loh et al (2009. Macromolecular Bioscience, 6:1069-1079).

The claims are drawn to a method of treating any of a number of cardiac disorders using a three-dimensional structure comprising ES cells, a mesenchymal stem cells, a hematopoietic stem cells, blood vessel stem cells or a synovial cells. The specification teaches treatment of cardiac damage resulting from ischemia using the claimed structure made using skeletal myoblasts. The specification does not teach treating any type of heart failure other than the effects of ischemia and does not teach use of any cells other than skeletal myoblasts.

The claims encompass use of multiple cell types. However, not all adult stem cells are capable of differentiating into cardiac muscle or in expressing muscle-specific factors that are essential in carrying out the claimed invention. Mathur and Martin reviewed the state of the art of stem cell therapy to treat cardiac myopathy resulting from ischemia (The Lancet, 2004, 264:183-192). At page 185 (col. 2) the different types of stem cells are discussed with regard to varying potencies of different stem cell types. Very few cells are considered totipotent, some are pluripotent while others are only multipotent or unipotent and are not capable of giving rise to any cell types. The claims broadly encompass multiple types of cell, including those that are known in the art to not give rise to cardiac cell types. The art, however, only supports treatment of the heart with cardiomyocytes, bone-marrow and blood progenitor cells and skeletal myoblasts (see pages 187-188). The claims now encompass use of a sheet of ES cells. However, the specification fails to support use of an ES cell in making the product of the invention. The specification teaches making cardiomyocytes from ES cells and culturing them on the temperature responsive macromolecule. Because ES cells need to be cultured on a feeder layer or an ECM and are

highly finicky with regard to their culture, it would be unpredictable that a sheet of ES could be made and used to carry out the method of treatment as claimed. In fact, the first report of ES cell culture on a temperature responsive polymer did not come until 2009 (see Loh et al) when conditions for making a copolymer including gelatin were established. Additionally, even upon formation of a sheet of ES cells or hematopoietic stem cells, there is no evidence of record or support demonstrating that these cells have the necessary therapeutic effect when applied to the heart.

With regard to the recitation of a "…wherein: the cell is…synovial cells", to the extent that the phrase reads on a single synovial cell, the claim is not enabled as the specification teaches use of a heterogenous population of cells isolated from the synovium. Within this population are stem cells as well as differentiated cells. The spec fails to establish which cells become part of the claimed sheet of cells and which ones are necessary for a therapeutic effect. Therefore, claims should not be limited to a single synovial cell.

As well, in general, the product claims read on a sheet of cells comprising only a single cell of the recited cell types. The specification fails to support that a single cell within a population would have a therapeutic effect.

Applicant has amended the claims to recite that the an ES cell, a mesenchymal stem cell, a hematopoietic stem cell, a blood vessel stem cell or synovial cells. The specification fails to provide support for use of these cells. The specification teaches the use of as sheet of either cardiomyocytes, skeletal myoblasts or synovial cells, each administered as a sheet. With regard to ES cells, the specification does not teach administration of a 3-dimensional structure comprising ES cells. The specification, at Example 6, teaches differentiating ES cells to form myoblasts and formation of a myoblast sheet.

The claims also encompass treatment of heart failure, which is broad and encompasses any type of heart disorder that causes the heart to fail. The claims also encompass myocarditis, which is inflammation of the heart. The specification and the art of record fail to teach treatment of the disorders encompassed by the claims. The only disorder the specification and the art of record address with the claimed methodology is myocardial infarction. Myocarditis is often caused by infection and is not marked by loss of cells treatable using stem cell therapy to lead to regeneration of lost tissue. It would require undue experimentation to determine how to treat, and which stem cell to us in treating, any heart disorder other than that relating to myocardial infarction.

With respect to this aspect of the rejection, Applicant argues that the specification states that a disease targeted by the present invention may be any heart disease in which tissue is injured. However, in response, the only tissue injury the cell sheet of the invention was actually applied to was a myocardial infarction model. Not all heart conditions will be treatable by the claimed method. For example, as set forth above, myocarditis is often caused by infection and is not marked by loss of cells treatable using stem cell therapy to lead to regeneration of lost tissue.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 9-16,18-21,23 and 27-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear. The phrase "having biological connection" at line 7 is unclear. It is not known what is intended to be encompassed by this phrase and the grammar is awkward. It is

not clear what is encompassed by "biological connection" and, as well, it is not clear what the connection is between.

Claim 1 is further unclear in use of the term “to water” in line . It is not known what a “lower critical solution temperature to water” is.

Claims 11-15 are unclear as they recite skeletal muscle-specific markers yet skeletal muscle cells are not encompassed in the breadth of parent claim 1. Thus, claims 11-15 fall outside the breadth of claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1-5,8-16,18,23 and 27 under 35 U.S.C. 102(b) as being anticipated by WO 01/07568 (published 02/01/2001) as evidenced by Carnac, G et al (1998, **Mol. Biol. Cell**., 9:1891-1902) is withdrawn in light of Applicant's amendments to the claims

The rejection of claims 1-5,8,11-17 and 19-23 remain rejected under 35 U.S.C. 102(b) as being anticipated by US 6,207,451 (March 27, 2001) as evidenced by Carnac, G et al (1998, **Mol. Biol. Cell**., 9:1891-1902) is withdrawn in light of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claim 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/07568 (published 02/01/2001) in view of Jin et al (Jour Pharm and Exp Therapeutics, 02/01/2003, 304:654-660) is withdrawn in light of Applicant's amendments to the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to VALARIE BERTOGLIO whose telephone number is (571)272-0725. The examiner can normally be reached on Mon-Fri 6:30-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/
Primary Examiner, Art Unit 1632